REMARKS

Reconsideration of the present Application in view of the present Amendments and the following remarks is respectfully requested. Claims 34-45 are currently pending. Applicants hereby cancel claims 34, 36-39, 41, 43, and 45 without acquiescence to any rejection and without prejudice to further prosecution of this subject matter in a related divisional, continuation, or continuation-in-part application. Applicants have amended claims 35, 40, 42, and 44 and added new claims 46 and 47 to define more clearly the subject matter that Applicants regard as their invention. Support for the amended claims may be found in the specification, for example, at page 4, lines 23-25; page 9, line 29 through page 10, line 6; page 19, line 29 through page 20, line 17; page 32, lines 20-25; and page 37, line 15 through page 38, line 5. The specification, specifically the Brief Description of Figure 1 and Figure 3, has been amended to describe that the Formal Drawings submitted herewith have several views. No new subject matter has been added.

OBJECTION TO THE DRAWINGS

The PTO objects to Figures 6-9 under 37 C.F.R. § 1.84 for alleged informalities. Specifically, the Draftsperson objects to Figure 6 under 37 C.F.R. § 1.84(b) (poor quality photograph); to Figures 7-8 under 37 C.F.R. § 1.84(e) (copy machine marks not accepted); and to Figure 9 under 37 C.F.R. § 1.84(g) (unacceptable top margin).

Applicants submit herewith corrected, Formal Drawings for Figures 6-9. Applicants respectfully submit that the corrected drawings comply with 37 C.F.R. § 1.84 and request that the objections be withdrawn. Applicants have also submitted Formal Drawings for Figures 1-5 and 10 with the present Amendment.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (WRITTEN DESCRIPTION)

The PTO rejects claims 36-45 under U.S.C. § 112, first paragraph, alleging that the claims are directed to subject matter that is not adequately described in the specification. In particular, the PTO alleges that the nucleic acid variants recited in the claims are defined only by function (reduction of T-lymphocyte proliferation in a non-human mammal) and that the claims

do not convey distinguishing information about the structural or physical characteristics of the DNA sequence. The PTO further asserts that the specification only discloses a single species and is insufficient to describe a broad genus.

Applicants respectfully traverse this rejection and submit that as disclosed in the specification and recited in the instant claims, Applicants possessed the claimed invention at the time the Application was filed. Applicants' invention is directed in pertinent part to a transgenic mouse whose cells express an *Fkh*^{sf} transgene that comprises a nucleic acid molecule comprising a nucleotide sequence that encodes an Fkh^{sf} polypeptide having the sequence set forth in SEQ ID NO:2 or that encodes an FKH^{sf} polypeptide having the sequence set forth in SEQ ID NO:4; to a transgenic mouse whose cells express an *Fkh*^{sf} transgene comprising a nucleic acid molecule encoding a polypeptide comprising the sequence of SEQ ID NO:2 or SEQ ID NO:4, wherein expression of the *Fkh*^{sf} transgene results in reduction of T-lymphocyte proliferation in the transgenic mouse compared to T-lymphocyte proliferation in a scurfy mouse; and to related compositions.

Applicants respectfully submit that the specification provides a detailed description of relevant and identifying characteristics of the claimed transgenic mouse. The present specification teaches the nucleotide sequences (SEQ ID NO:1 and SEQ ID NO:3) that encode the wildtype *Fkh*^{sf} gene products, murine Fkh^{sf} polypeptide (SEQ ID NO:2) and its human homologue FKH^{sf} polypeptide (SEQ ID NO:4), respectively. The specification also discloses that a two base insertion (*sf* mutation) in the *Fkh*^{sf} gene results in an immune system disorder, which is manifested as the scurfy phenotype observed in affected animals (*see, e.g.*, at page 1, line 24 through page 2, line 13; page 6, lines 6-9; page 9, line 29 through page 10, line 6 and references cited therein; pages 32-33 (Example 1); pages 35-36 (Example 4)).

The specification describes that wildtype *Fkh*^{sf} gene products may be expressed in a transgenic animal whose germ cells and somatic cells contain polynucleotide sequences that encode the Fkh^{sf} proteins (*see, e.g.,* page 19, line 29 through page 20, line 17; Example 1). The specification further describes that each transgenic mouse made by injecting normal mouse one-cell embryos with genomic DNA containing the wildtype *Fkh*^{sf} gene has distinct integrations of the gene (*see* Example 1, page 33). Relevant, identifying characteristics of these transgenic

animals include a number of immune competence parameters (*see, e.g.,* page 37-38, Example 8). As described in the specification, in the absence of any stimulation, the proliferation of T lymphocytes from mice expressing the *Fkh*^{sf} transgene is reduced when compared to T cell proliferation in scurfy mice (*see, e.g.,* page 37, line 28 through page 38, line 5; Figure 8). In the presence of T lymphocyte stimulation, such as reacting the cells with antibodies that bind to CD3 and CD28 cell surface receptors, T lymphocyte responsiveness of the transgenic mice to the stimulation is reduced compared to the responsiveness of T cells from normal animals and from scurfy mice (*see, e.g., id.*). These transgenic mice also have a reduced number of lymphoid cells in their lymph nodes (*see, e.g.,* page 37, lines 22-23; Figure 7).

Applicants also respectfully submit that the instant specification describes relevant identifying characteristics of a transgenic mouse, whose cells express an *Fkh*^{sf} transgene comprising a nucleic acid molecule comprising a sequence at least 90% identical to the coding region of SEQ ID NO:1 (*see, e.g.,* page 11, lines 11-30; page 12, lines 6-13; Examples 1 and 8). Nevertheless, solely to expedite prosecution of this case and without acquiescing to the rejection, Applicants have cancelled claims 36-39, 41, 43, and 45, rendering the rejection of these claims moot.

Accordingly, Applicants respectfully submit that the presently claimed subject matter is sufficiently described by the specification to reasonably convey to a person skilled in the art that Applicants possessed the claimed invention at the time the Application was filed. Applicants therefore submit that the instant Application complies with the written description requirement under 35 U.S.C. § 112, first paragraph, and respectfully request that the rejection be withdrawn.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (ENABLEMENT)

The PTO rejects claims 34-45 under 35 U.S.C. § 112, first paragraph, for lack of enablement. The PTO concedes that the specification enables a transgenic Scurfy mouse whose somatic and germ cells express a transgene comprising a 30 kb fragment of normal genomic DNA that includes the coding region of an *Fkh*^{sf} gene as well as upstream and downstream flanking sequences. The PTO asserts, however, that the specification does not reasonably

provide enablement for any transgenic mouse, rat, rabbit, sheep, goat, or pig whose cells express a *Fkh*^{sf} transgene comprising a mouse *Fkh*^{sf} polynucleotide (SEQ ID NO:1) or a human *FKH*^{sf} polynucleotide (SEQ ID NO:3), wherein the expression of the *Fkh*^{sf} transgene results in reduction of T-lymphocyte proliferation in the mammal. Specifically, the PTO alleges that the specification does not enable a skilled artisan to make and use the claimed invention commensurate with the scope of the claims, without undue experimentation.

Applicants respectfully traverse this rejection and submit that as disclosed in the present specification and recited in the instant claims, Applicants fully enabled the claimed invention at the time the instant Application was filed. Applicants respectfully submit that, contrary to the assertion in the Action and for reasons already made of record, the instant specification enables a skilled artisan to make and use a transgenic non-human mammal whose cells express a *Fkh*^{sf} transgene that comprises a nucleic acid molecule comprising a sequence at least 90% identical to the coding region of SEQ ID NO:1 or SEQ ID NO:3, wherein expression of the *Fkh*^{sf} transgene results in reduction of T-lymphocyte proliferation in the mammal. Nevertheless, solely to expedite prosecution of this subject matter and without acquiescing to the rejection, Applicants have cancelled claims 34, 36-39, 41, 43, and 45, rendering the rejection of these claims moot.

Applicants respectfully submit that the specification provides ample guidance enabling a skilled artisan to make and use the presently claimed transgenic mouse readily and without undue experimentation. As noted above, Applicants' invention is directed in pertinent part to a transgenic mouse whose cells express an *Fkh*^{sf} transgene that comprises a nucleic acid molecule comprising a nucleotide sequence that encodes an Fkh^{sf} polypeptide (SEQ ID NO:2) or that encodes an FKH^{sf} polypeptide (SEQ ID NO:4); and to such a transgenic mouse, wherein expression of the *Fkh*^{sf} transgene results in reduction of T-lymphocyte proliferation in the transgenic mouse compared to T-lymphocyte proliferation in a scurfy mouse. As taught in the present specification, nucleotide sequences (SEQ ID NO:1 and SEQ ID NO:3) encode the wildtype *Fkh*^{sf} gene products, murine Fkh^{sf} polypeptide (SEQ ID NO:2) and its human homologue FKH^{sf} polypeptide (SEQ ID NO:4), respectively. The specification enables a skilled artisan to make transgenic mice whose cells express an *Fkh*^{sf} transgene encoding a wildtype gene

product by injecting pronuclei of normal mouse one-cell embryos with genomic DNA that contains the *Fkh*^{sf} gene according to methods known in the art and described in the specification (*see, e.g.*, page 19, line 29 through page 20, line 17; Example 1, page 33, lines 10-14). Integration of the injected DNA can be detected by methods known in the art, such as dot blot analysis of DNA from tissue samples (*see, e.g.*, page 20, lines 9-14).

The instant specification also provides enabling guidance to a skilled artisan to analyze parameters related to the immune competence of the subject invention transgenic mice that express the *Fkh*^{sf} transgene (*see, e.g.*, page 37, line 15 through page 38, line 5). For example, proliferation of T lymphocytes in the absence and presence of stimulation, such as reacting T cells with antibodies that bind to CD3 and CD28 cell surface receptors, may be determined according to techniques known in the art and taught in the specification (*see, e.g.*, page 37, line 15 through page 38, line 5). In addition, transgenic animals may be examined for the size of and number of cells in lymphoid organs such as the thymus and lymph node (*id.*).

The specification teaches that a two base insertion (*sf* mutation) in the *Fkh*^{sf} gene results in an immune system disorder, which is manifested as the scurfy phenotype observed in affected animals (*e.g.*, at page 1, line 24 through page 2, line 13; page 6, lines 6-9; page 9, line 29 through page 10, line 6 and references cited therein; page 32 through page 33 (Example 1)). As known in the art and described in the specification, the scurfy mutation is an X-linked mutation, and males hemizygous (X^{sf}/Y) for the scurfy mutation exhibit the severe lymphoproliferative disorder (*see, e.g.*, page 1, lines 24-27). While the T cells of such scurfy mice proliferate well in the absence of stimulation, T lymphocytes of the subject invention transgenic mice exhibit a response similar to the response observed with normal T cells, which is a reduction in T lymphocyte proliferation compared to the scurfy mice.

Applicants respectfully submit that in view of the direction and guidance provided by the instant specification, which includes working examples, the present specification enables a skilled artisan to make and use the subject invention transgenic mice readily and without undue experimentation. Applicants therefore submit that the present Application meets the requirements of 35 U.S.C. § 112, first paragraph and respectfully request that the rejection of the claims be withdrawn.

Applicants respectfully submit that all claims remaining in the Application are now allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

Mary E. Brunkow et al.

SEED Intellectual Property Law Group PLLC

Mae Joanne Rosok
Registration No. 48,903

Enclosure: 11 sheets of Formal Drawings, Figures 1A - 10

701 Fifth Avenue, Suite 6300
Seattle, Washington 98104-7092
Phone: (206) 622-4900
Fax: (206) 682-6031

MJR:lmp 401400v2